Application Ser. No.: 10/721,210
Filing Date: November 25, 2003
Examiner: Davis, Zinna Northington

Amendment Pursuant to 37 C.F.R. § 1.121

IN THE CLAIMS:

The claims set forth below with amendments as indicated will replace all prior versions and listing of claims in the application.

1 (currently amended) A compound corresponding to the following formula:

nitrogen-containing aromatic ring – $(NR_3)p$ – $(CO)n$- distribution agent – $(CO)m$ – $(NR'_3)q$ – aromatic or non-aromatic ring

wherein
n, m, p and q are 1; and wherein

- the nitrogen-containing aromatic ring is:
  - ◊ a quinoline optionally substituted with at least
    - one group N(Ra)(Rb) in which Ra and Rb, are identical or different, and are independently of each other hydrogen or a C1-C4 alkyl; or
    - one C1-C4 alkyl or alkoxy;
  - ◊ a quinoline possessing a nitrogen atom in quaternary form;

or

  - ◊ a pyridine;
- the aromatic or non-aromatic ring is:
  - ◊ a quinoline optionally substituted with at least
    - one group N(Ra)(Rb) in which Ra and Rb, are identical or different, and are independently hydrogen or a C1-C4 alkyl; or
    - one C1-C4 alkyl or alkoxy;
  - ◊ a quinoline possessing a nitrogen atom in quaternary form;
  - ◊ a pyridine; or
  - ◊ a phenyl optionally substituted with halogen, C1-C4 alkoxy, cyano, carbonylamino optionally substituted with one or

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more C1-C4 alkyl, guanyl, C1-C4 alkylthio, amino, C1-C4 alkylamino, C1-C4 dialkylamino, nitro, C1-C4 alkyleneamino or C2-C4 alkenyleneamino;

- R_3 and R'_3, which are identical or different, represent independently of each other hydrogen or C1-C4 alkyl;
- the distribution agent is:
  - ◊ a triazine group optionally substituted with one or more radicals chosen from halogen, C1-C4 alkyl, and thio, oxy or amino which are themselves optionally substituted with one or more C1-C4 alkyl;
  - ◊ a 5- or 6-membered heterocyclic radical containing a sulfur, oxygen or nitrogen atom;
  - ◊ a phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-, -NH-CH2-phenyl-NH-, -CH2-phenyl-CH2-, -CH2-phenyl, -phenyl-CH2-, -CH2-thienyl-, -thienyl-CH2-, or -CH=CH-~~; or
  - ◊ a diazine group; and wherein

  the heterocyclic, phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-, -NH-CH2-phenyl-NH-, -CH2-phenyl-CH2-, -CH2-phenyl, -phenyl-CH2-, -CH2-thienyl-, -thienyl-CH2-, -CH=CH-,~~ and diazine are optionally substituted with the same groups as the triazine;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that:

when the distribution agent is 2,5-pyridyl, 2,6-pyridyl, 2,5-furanyl or phenyl ~~optionally~~ unsubstituted or substituted with NH_2~~, 2,5-pyridyl or 2,6-pyridyl~~ or 2-chloro, and R_3 and R'_3 are hydrogen, then the nitrogen-containing aromatic ring and the aromatic ring are not both quinoline which is unsubstituted or substituted with C1-C4 alkyl.

2 (original) The compound according to claim 1 which binds the G-quadruplex structure of telomeres.

3 (currently amended) The compound according to claim 1 wherein the

distribution agent is chosen from the heterocyclic group, phenyl, ~~-NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-, -NH-CH2-phenyl-NH-, -CH2-phenyl-CH2-, -CH2-phenyl-, -phenyl-CH2-, -CH2-thienyl-, -thienyl-CH2-, -CH=CH-~~ and diazine.

4 - 6 (canceled)

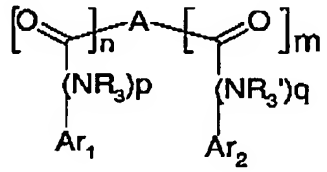
7 (original) The compound according to claim 1 wherein the distribution agent is thienyl or pyridyl.

8 (currently amended) The compound according to claim 1 wherein the distribution agent is chosen from thienyl, pyridyl, phenyl, ~~-NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-~~ and diazine.

9 (original) The compound according to claim 1 wherein the diazine group is a pyrimidine.

10 (canceled)

11 (currently amended) The compound according to claim 1 having the following formula (IA) :



(IA)

wherein

n, m, p and q are 1;

- A represents:
  - ◊ a 5- to 6-membered heterocyclic radical containing a sulfur, oxygen or nitrogen atom;
  - ◊ a phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-, -NH-CH2-phenyl-NH-, -CH2-phenyl-CH2-,~~

~~-CH2-phenyl, -phenyl-CH2-, -CH2-thienyl-, -thienyl-CH2- or -CH=CH-~~;
or

◊ a diazine group; and wherein

the heterocyclic, phenyl, ~~-NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-, -NH-CH2-phenyl-NH-, -CH2-phenyl-CH2-, -CH2-phenyl-, -phenyl-CH2-, -CH2-thienyl-, -thienyl-CH2-, -CH=CH-,~~ and diazine are optionally substituted with one or more radicals chosen from halogen, C1-C4 alkyl, and thio, oxy or amino which are themselves optionally substituted with one or more C1-C4 alkyl;

- R_3 and R'_3, which are identical or different, represent independently of each other hydrogen or C1-C4 alkyl;
- Ar_1 and Ar_2, which are identical or different, and are independently of each other selected from:
  - a quinoline optionally substituted with at least
    - a group N(Ra)(Rb) in which Ra and Rb are identical or different, and are independently of each other hydrogen or a C1-C4 alkyl; or
    - a C1-C4 alkyl or alkoxy;
  - a quinoline possessing a nitrogen atom in quaternary form;
  - a pyridine optionally attached at the 4-position or fused with an aryl or heteroaryl group, optionally substituted with a C1-C4 alkyl; or
  - a phenyl optionally substituted with halogen, C1-C4 alkoxy, cyano, carbonylamino optionally substituted with one or more C1-C4 alkyl, guanyl, C1-C4 alkylthio, amino, C1-C4 alkylamino, C1-C4 dialkylamino, nitro, C1-C4 alkyleneamino or C2-C4 alkenyleneamino;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that:

when A is 2,5-pyridyl, 2,6-pyridyl, 2,5-furanyl or phenyl ~~optionally~~ unsubstituted or substituted with NH_2, ~~2,5-pyridyl or 2,6-pyridyl~~ or 2-chloro, and when R_3 and R_3' are hydrogen, then Ar_1 and Ar_2 are not both

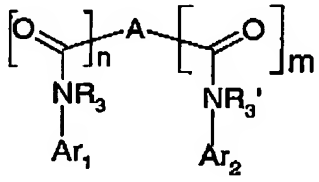
quinoline which is unsubstituted or substituted ~~on its nitrogen atom~~ with C1-C4 alkyl.

12 (currently amended) The compound according to claim 11 wherein A is chosen from heterocyclic group, phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-, -NH-CH2-phenyl-NH-, -CH2-phenyl-CH2-, -CH2-phenyl, -phenyl-CH2-, -CH2-thienyl-, -thienyl-CH2-, -CH=CH-~~ and pyrimidine.

13 - 14 (canceled)

15 (original) The compound according to claim 11 wherein the diazine group which A may represent is pyrimidine.

16 (currently amended) The compound according to claim 1 having the following formula (I) :



(I)

wherein
n and m are 1;

- A represents:
  - ◊ a 5- to 6-membered heterocyclic radical containing a sulfur, oxygen or nitrogen atom;
  - ◊ a phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH- or -NH-CH2-phenyl-CH2-NH-~~; or
  - ◊ a diazine group; and wherein

  the heterocyclic, phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-,~~ and diazine are optionally substituted with one or more radicals chosen from halogen, C1-C4 alkyl, and thio, oxy or amino which are themselves optionally substituted with one or more C1-C4 alkyl;

- R_3 and R'_3, which are identical or different, represent independently of each other hydrogen or C1-C4 alkyl;

- Ar_1 and Ar_2, which are identical or different, and are independently of each other selected from :

  - a quinoline optionally substituted with at least
    - a group N(Ra)(Rb) in which Ra and Rb are identical or different, and are independently of each other hydrogen or a C1-C4 alkyl; or
    - a C1-C4 alkyl or alkoxy;
  - a quinoline possessing a nitrogen atom in quaternary form;
  - a pyridine optionally attached at the 4-position or fused with an aryl or heteroaryl group, optionally substituted with a C1-C4 alkyl; or
  - a phenyl optionally substituted with halogen, C1-C4 alkoxy, cyano, carbonylamino optionally substituted with one or more C1-C4 alkyl, guanyl, C1-C4 alkylthio, amino, C1-C4 alkylamino, C1-C4 dialkylamino, nitro, C1-C4 alkyleneamino or C2-C4 alkenyleneamino;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that:

when A is 2,5-pyridyl, 2,6-pyridyl, 2,5-furanyl or phenyl ~~optionally~~ unsubstituted or substituted with NH_2, ~~2,5-pyridyl or 2,6-pyridyl~~ or 2-chloro, and when R_3 and R_3' are hydrogen, then Ar_1 and Ar_2 are not both quinoline which is unsubstituted or substituted with C1-C4 alkyl.

17 (currently amended) The compound according to claim 16 wherein A is chosen from thienyl, pyridyl, phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-~~ and pyrimidine.

18 (canceled)

19 (original) The compound according to claim 16 wherein Ar_1 and Ar_2 represent:

- a quinoline optionally substituted with at least
  - a group N(Ra)(Rb) in which Ra and Rb are identical or different, and are independently of each other hydrogen or C1-C4 alkyl; or
  - a C1-C4 alkyl or alkoxy;
- a quinoline possessing a nitrogen atom in quaternary form; or
- pyridine.

20 (original) The compound according to claim 16 wherein Ar_1 and Ar_2 are chosen from the following groups : 4-amino-, 4-methylamino-, 4-dimethylamino- or 4-alkoxy-quinolyl or -quinolinium in which the quinolinium is optionally substituted with one or two methyl groups.

21 (original) The compound according to claim 16 wherein A is optionally substituted with one or more radicals chosen from halogen, C1-C4 thioalkyl, amino, C1-C4 alkylamino or C1-C4 dialkylamino.

22 (original) The compound according to claim 16 wherein A is optionally substituted with methylthio or halogen.

23 – 24 (canceled)

25 (currently amended) The compound of formula (IA) according to claim 11 wherein:

~~n, m, p and q are 1;~~

- A represents:
  - ◊ thienyl or pyridyl;
  - ◊ phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-, -CH2-phenyl-CH2- or -CH=CH-~~; or
  - ◊ pyrimidyl optionally substituted with one or more radicals chosen from halogen or C1-C4 alkylthio;

- R_3 and R'_3, which are identical or different, represent independently of each other hydrogen or C1-C4 alkyl;
- Ar_1 and Ar_2, which are identical or different, and are independently of

each other selected from :

- a quinoline optionally substituted with at least
  - a group N(Ra)(Rb) in which Ra and Rb are identical or different, and are independently of each other hydrogen or C1-C4 alkyl; or
  - a C1-C4 alkyl or alkoxy;
- a quinoline possessing a nitrogen atom in quaternary form; or
- a pyridyl;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof.

26 (currently amended) The compound of formula (IA) according to claim 11 wherein:

- A represents:
  - ◊ thienyl or pyridyl;
  - ◊ phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH- or -NH-CH2-phenyl-CH2-NH-~~; or
  - ◊ pyrimidyl optionally substituted with one or more radicals chosen from halogen or C1-C4 alkylthio;
- R_3 and R'_3, which are identical or different, represent independently of each other hydrogen or C1-C4 alkyl;
- Ar_1 and Ar_2, which are identical or different, and are independently of each other selected from :
  - a quinoline optionally substituted with at least
    - a group N(Ra)(Rb) in which Ra and Rb, which are identical or different, and are independently of each other hydrogen or C1-C4 alkyl; or
    - a C1-C4 alkyl or alkoxy;
  - a quinoline possessing a nitrogen atom in quaternary form; or
  - a pyridyl;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof.

27 (original) The compound according to claim 26 wherein Ar_1 and Ar_2, which are identical or different, and are independently of each other chosen from the 4-amino-, 4-methylamino-, 4-dimethylamino- or 4-alkoxy-quinolyl or -quinolinium groups in which the quinolinium is optionally substituted with one or two methyl groups.

28 (original) The compound according to claim 26 wherein R_3 and R_3' represent hydrogen.

29 (previously presented) The compound according to claim 26 wherein :

1. Ar_1 represents :
   - a quinoline substituted with at least
     - one group N(Ra)(Rb) in which Ra and Rb are identical or different, and are independently of each other hydrogen or C1-C4 alkyl; or
     - a C1-C4 alkyl or alkoxy;
   - a quinoline possessing a nitrogen atom in quaternary form; and
2. Ar_2 represents
   - a quinoline substituted with at least
     - one group N(Ra)(Rb) in which Ra and Rb are identical or different, and are independently of each other hydrogen or C1-C4 alkyl; or
     - a C1-C4 alkyl or alkoxy;
   - a quinoline possessing a nitrogen atom in quaternary form; or
   - a pyridyl;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof.

30 (currently amended) The compound of formula (IA) according to claim 11 chosen from :

- bis[(4-methoxy-2-methylquinolin-6-yl)-amido]-2,5-thiophenedicarboxylic acid;
- bis[(4-dimethylamino-2-methylquinolin-6-yl)-amido]-2,5-

thiophenedicarboxylic acid;
- bis[(4-amino-2-methylquinolin-6-yl)-amido]-2,5-thiophenedicarboxylic acid;
- N,N'-bis(4-amino-2-methylquinolin-6-yl)isophthalamide;
- N,N'-bis(4-dimethylamino-2-methylquinolin-6-yl)terephthalamide;
~~- 1-(4-methoxy-2-methylquinolin-6-yl)-3-{3-[3-(4-methoxy-2-methylquinolin-6-yl)ureido]phenyl}urea;~~
~~- 1-(4-dimethylamino-2-methylquinolin-6-yl)-3-{4-[3-(4-dimethylamino-2-methylquinolin-6-yl)ureido]phenyl}urea;~~
~~- N,N'-bis(4-amino-2-methyl-6-quinolyl)-2,4-diamino-6-chloro-5-methyl-sulfanylpyrimidine;~~
- bis[(4-amino-2-methyl-quinolin-6-yl)-amido]-2,5-pyridinedicarboxylic acid hydrochloride;
~~- bis[(4-amino-2-methylquinolin-6-yl)-amido]-2,5-pyridinedicarboxylic acid;~~
~~- N,N'-bis(4-dimethylamino-2-methylquinolin-6-yl)-but-2-enediamide;~~
- bis[(4-dimethylamino-2-methyl-quinolin-6-yl)-amido]-2,5-pyridinedicarboxylic acid;
- bis[(4-dimethylamino-2-methylquinolin-6-yl)-amido]-2,4-pyridinedicarboxylic acid;
~~- N,N'-bis(4-dimethylamino-2-methylquinolin-6-yl)-1,4-phenylenediacetamide;~~
- bis[(4-amino-2-methyl-quinolin-6-yl)-amido]-2,6-pyridinedicarboxylic acid hydrochloride;
- bis[(4-amino-2-methyl-quinolin-6-yl)amido]-2,6-pyridine dicarboxylic acid;
- bis[(4-dimethylamino-2-methylquinolin-6-yl)amido]-2,6-pyridinedicarboxylic acid hydrochloride; and
- bis[(4-dimethylamino-2-methylquinolin-6-yl)-amido]-2,6-pyridinedicarboxylic acid;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof.

31 (currently amended) The compound according to claim 30 chosen from :
- bis[(4-dimethylamino-2-methylquinolin-6-yl)-amido]-2,5-

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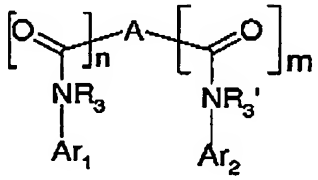
thiophenedicarboxylic acid;
- N,N'-bis-(4-amino-2-methylquinolin-6-yl)isophthalamide;
~~- 1-(4-dimethylamino-2-methylquinolin-6-yl)-3-[4-[3-(4-dimethylamino-2-methyl-quinolin-6-yl)ureido]phenyl]urea;~~
~~- N,N'-bis(4-amino-2-methyl-6-quinolyl)-2,4-diamino-6-chloro-5-methyl-sulfanylpyrimidine;~~
- bis[(4-amino-2-methylquinolin-6-yl)-amido]-2,5-pyridinedicarboxylic acid hydrochloride;
- bis[(4-amino-2-methylquinolin-6-yl)-amido]-2,5-pyridinedicarboxylic acid;
- bis-[(4-dimethylamino-2-methylquinolin-6-yl)-amido]-2,5-pyridinedicarboxylic acid; and
- bis[(4-dimethylamino-2-methylquinolin-6-yl)amido]-2,4-pyridinedicarboxylic acid;
or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof.

32 (currently amended) A pharmaceutical composition comprising therapeutically effective amount of a compound of formula (I) in combination with a pharmaceutically acceptable carrier ;



(I)

wherein
n and m are 1;
- A represents:
  - ◊ a 5- to 6-membered heterocyclic radical containing a sulfur, oxygen or nitrogen atom;
  - ◊ a phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH- or -NH-CH2-phenyl-CH2-NH-~~; or
  - ◊ a diazine group; and wherein

the heterocyclic, phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-,~~ and diazine are optionally substituted with

one or more radicals chosen from halogen, C1-C4 alkyl, and thio, oxy or amino which are themselves optionally substituted with one or more C1-C4 alkyl;

- R_3 and R'_3, which are identical or different, represent independently of each other hydrogen or C1-C4 alkyl;
- Ar_1 and Ar_2, which are identical or different, and are independently of each other selected from :
  - a quinoline optionally substituted with at least
    - a group N(Ra)(Rb) in which Ra and Rb are identical or different, and are independently of each other hydrogen or a C1-C4 alkyl; or
    - a C1-C4 alkyl or alkoxy;
  - a quinoline possessing a nitrogen atom in quaternary form;
  - a pyridine optionally attached at the 4-position or fused with an aryl or heteroaryl group, optionally substituted with a C1-C4 alkyl; or
  - a phenyl optionally substituted with halogen, C1-C4 alkoxy, cyano, carbonylamino optionally substituted with one or more C1-C4 alkyl, guanyl, C1-C4 alkylthio, amino, C1-C4 alkylamino, C1-C4 dialkylamino, nitro, C1-C4 alkyleneamino or C2-C4 alkenyleneamino;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that:

when A is 2,5-pyridyl, 2,6-pyridyl, 2,5-furanyl or phenyl ~~optionally~~ unsubstituted or substituted with NH_2, ~~2, 5-pyridyl or 2,6-pyridyl~~ or 2-chloro, and when R_3 and R_3' are hydrogen, then Ar_1 and Ar_2 are not both quinoline which is unsubstituted or substituted with C1-C4 alkyl.

33 (original) The composition according to claim 32 which further comprises an anticancer agent.

34 (original) The composition according to claim 33 wherein the anticancer

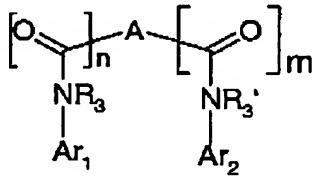
agent is chosen from alkylating agents, platinum derivatives, antibiotic agents, antimicrotubule agents, anthracyclines, group I and II topoisomerases, fluoropyrimidines, cytidine analogues, adenosine analogues, L-asparaginase, hydroxyurea, trans-retinoic acid, suramine, irinotecan, topotecan, dexrazoxane, amifostine, herceptin, oestrogenic and androgenic hormones and antivascular agents.

35 (original) The composition according to claim 32 used in conjunction with radiation treatment.

36. (original) The composition according to claim 33 wherein each of the components is administered simultaneously, separately or sequentially.

37. (original) The composition according to claim 35 wherein the compound and the radiation treatment are administered simultaneously, separately or sequentially.

38. (currently amended) A method of treatment of a cancer in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula (I):



(I)

wherein
n and m are 1;

- A represents:
  - ◊ a 5- to 6-membered heterocyclic radical containing a sulfur, oxygen or nitrogen atom;
  - ◊ a phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH- or -NH-CH2-phenyl-CH2-NH-~~; or
  - ◊ a diazine group; and wherein

  the heterocyclic, phenyl~~, -NH-phenyl-NH-, -NH-phenyl-CH2-NH-, -NH-CH2-phenyl-CH2-NH-,~~ and diazine are optionally substituted with

one or more radicals chosen from halogen, C1-C4 alkyl, and thio, oxy or amino which are themselves optionally substituted with one or more C1-C4 alkyl;

- R_3 and R'_3, which are identical or different, represent independently of each other hydrogen or C1-C4 alkyl;
- Ar_1 and Ar_2, which are identical or different, and are independently of each other selected from :
  - a quinoline optionally substituted with at least
    - a group N(Ra)(Rb) in which Ra and Rb are identical or different, and are independently of each other hydrogen or a C1-C4 alkyl; or
    - a C1-C4 alkyl or alkoxy;
  - a quinoline possessing a nitrogen atom in quaternary form;
  - a pyridine optionally attached at the 4-position or fused with an aryl or heteroaryl group, optionally substituted with a C1-C4 alkyl; or
  - a phenyl optionally substituted with halogen, C1-C4 alkoxy, cyano, carbonylamino optionally substituted with one or more C1-C4 alkyl, guanyl, C1-C4 alkylthio, amino, C1-C4 alkylamino, C1-C4 dialkylamino, nitro, C1-C4 alkyleneamino or C2-C4 alkenyleneamino;

or an isomer, an enantiomer, a diastereoisomer or a mixture thereof, or a pharmaceutically acceptable salt thereof;

with the proviso that:

when A is 2,5-pyridyl, 2,6-pyridyl, 2,5-furanyl or phenyl ~~optionally~~ unsubstituted or substituted with NH_2, ~~2, 5-pyridyl or 2,6-pyridyl~~ or 2-chloro, and when R_3 and R_3' are hydrogen, then Ar_1 and Ar_2 are not both quinoline which is unsubstituted or substituted with C1-C4 alkyl.